REMARKS/ARGUMENTS

Status of the Claims

Claims 1-22 are pending in the application.

Claims 1-15 are rejected.

Claims 16-22 are new. Support for claims 16-21 can be found on page 6, line 27 to page 7, line 10.

Claims 1, 2, 4-7, 11 and 13-15, have been amended. Support for the amendment can be found on page 3, lines 22 & 23; page 5, line 25; page 6, line 26 to page 7, line 15; and page 10, lines 3-12.

Rejection Under 35 U.S.C. § 103

Claims 1, 4-9, and 13-15 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Powell et al., U.S. Patent No. 3,793,454 ("Powell") in view of D'Amato et al., U.S. Patent No. 5,712,291 ("D'Amato") and Kawai et al., Cancer Lett. 2001 Oct. 10; 171(2):201-07 ("Kawai"), and in further view of Powell et al., J. Pharmaceutical Sciences, August 1972 61(8):1227-1230 ("Powell II").

In order to make a proper obviousness rejection, the Examiner is required to establish a *prima facie* case by analyzing the *Graham* factors and providing reasons why "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." *KSR Int'l. Co. v. Teleflex*, 127 S.Ct. 1727 (2007). Merely demonstrating that each of the elements of a claim is independently known in the prior art is not sufficient to prove that the claim is obvious. *Id.* at 1741. Rather, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.*; see also *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references.").

Claim 1 as amended recites "a method of treating a host with an angiogenic disease, consisting essentially of contacting said host with a cephalotaxine in an amount sufficient to inhibit angiogenesis associated with said angiogenic disease, wherein said angiogenic disease is not a solid tumor and wherein said angiogenesis associated with

said angiogenic disease is inhibited in said host." Claim 7 also recites that angiogenesis associated with said angiogenic disease is inhibited in said host.

Powell in view of D'Amato, Kawai and Powell II does not teach or suggest the claimed invention. Powell discloses the implantation of leukemic strains L1210 and P388 into mice, which were treated with intraperitoneal injections of a cephalotaxine. Powell does not disclose that angiogenesis is associated with these implanted leukemic cell strains. Powell also does not disclose that angiogenesis associated with an angiogenic disease is inhibited as recited in the amended claims.

The Examiner states that

> "the broader, instructive disclosure of Powell which makes clear that the active disclosed can be used for the treatment of leukemia is more than sufficient to establish a *prima facie* case of obviousness. Further, Powell et al. clearly discloses sufficient information that one of ordinary skill in the art would have recognized the clinical usefulness of the invention of Powell in treating leukemia."

Applicant, however, submits that the Examiner has read Powell too broadly in that Powell does not teach treating leukemia generally. Powell discloses that mice that were implanted with either lymphoid leukemia L1210 or lymphocytic leukemia P388 and that received intraperitoneal injections of harringtonine survived longer than untreated mice. Assuming *arguendo* that angiogenesis is associated with myelogenous leukemia, Powell does not teach or suggest that the leukemic cell lines of Powell migrated to the bone marrow and that vascularization in the bone marrow was inhibited. At best, Powell shows that mice that had an ascites suspension of leukemia cells and that were treated intraperitoneally with a cephalotaxine survived longer than mice that were untreated. Powell does not teach or suggest that the administered harringtonine or isoharringtonine led to the inhibition of angiogenesis associated with leukemia. Powell is therefore properly read to disclose the use of harringtonine or isoharringtonine in the treatment of implanted, ascitic, leukemic tumor cells, not myelogenous leukemia of the bone marrow and blood or leukemia generally. Powell does not teach or suggest contacting a host with a cephalotaxine to inhibit angiogenesis associated with an angiogenic disease.

Powell in combination with the secondary references cited by the Examiner provides no reason or motivation for contacting a host with a cephalotaxine to inhibit angiogenesis associated with an angiogenic disease. Powell II does not show that "harringtonine, isoharringtonine, homoharringtonine and deoxyharringtonine were known in the art as being effective against leukemia" as the Examiner contends. Powell II in the

abstract states that those compounds have shown significant activity against "experimental P388 leukemia and against L-1210 leukemia in mice." Otherwise directed toward structural studies of cephalotaxines, Powell II is cumulative to the teachings of Powell, since it too only teaches that certain cephalotaxines may be useful against implanted, ascitic leukemia tumor cells, not against leukemia generally.

D'Amato teaches that angiogenesis has been associated with blood-borne tumors such as leukemias. However, Powell discloses the administration of homoharringtonine to treat ascitic tumor cells. Thus, although angiogenesis in the bone marrow may be associated with leukemia, as taught by D'Amato, Powell, properly read, does not teach the administration of a cephalotaxine to treat such leukemias. As stated above, Powell teaches the administration of a cephalotaxine to treat a population of implanted, ascitic cells. As such, considering Powell in view of D'Amato, one of skill in the art would not have arrived at the presently claimed invention, which requires contacting a host with a cephalotaxine and inhibiting angiogenesis associated with an angiogenic disease.

Kawai provides no reason for contacting a host with a cephalotaxine and inhibiting angiogenesis associated with an angiogenic disease. Kawai simply teaches that one type of leukemia cell line, THP-1, is non-solid (see abstract and page 202, paragraph 1). This teaching, in combination with the other references, does nothing to show why one of skill in the art would contact a host with a cephalotaxine such that angiogenesis associated with an angiogenic disease is inhibited.

The Examiner has provided no reasons why the combined references teach or suggest the claimed invention to one of skill in the art. The Examiner has therefore not established a prima facie case of obviousness, and withdrawal of the rejection is respectfully requested.

Claims 1-15 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chinery et al., U.S. Patent Application Publication No. 2001/0049349 ("Chinery") in view of D'Amato et al., U.S. Patent No. 5,712,291 ("D'Amato"); Cecil *Textbook of Medicine*, pp. 1060-1074 ("Cecil"), O'Dwyer et al., *J. Clin. Oncol.*, 4:10(October), 1986, pp. 1563-1568 ("O'Dwyer") and Medford et al., U.S. Patent No. 5,380,747 ("Medford"), and in further view of Powell II. Applicants respectfully disagree.

Chinery, cited by the Examiner as the primary reference, is directed toward the use of antioxidants "to enhance the efficacy of antineoplastic drugs for the treatment of abnormal cell proliferation." See Chinery, ¶ 15. Chinery discloses the administration of

an antineoplastic drug in combination with an antioxidant. Claim 1, however, now recites a method of treating a host with an angiogenic disease "consisting essentially of" contacting said host with a cephaloxine, wherein angiogenesis associated with said angiogenic disease is inhibited. The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps and "those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. MPEP 2111.03.

Chinery teaches that antioxidants "enhance the efficacy of antineoplastic drugs" and are "cytotoxicity-increasing." Chinery, ¶¶ 15 & 59. Chinery therefore teaches that the disclosed antioxidants would materially affect the basic and novel characteristics of antineoplastic drugs, which include homoharringtonine. In view of the limiting effect of the transitional phrase "consisting essentially of," the scope of the present claims excludes administering a cephalotaxine in combination with an antioxidant.

Thus, among other differences, Chinery requires the use of an antioxidant to enhance the cytotoxic effect of an antineoplastic, while the present claims exclude such use in the inhibition of angiogenesis associated with an angiogenic disease. The Examiner has provided no reason why this difference is such that the present claims are obvious. In other words, the question that the Examiner must answer is why the present claims, which exclude the use of an antioxidant in the inhibition of angiogenesis associated with an angiogenic disease, are obvious in view of the cited references combined with Chinery, which requires an antioxidant and makes no mention of inhibiting angiogenesis. The Examiner stated on page 5 of the Office Action of July 5, 2007, that "whether an antioxidant is administered or not, the present method would be effective for the inhibition of angiogenesis." This is not what Chinery or any of the references teaches; rather, Chinery teaches administering "an antineoplastic drug to a host exhibiting abnormal cell proliferation *in combination with* an effective cytotoxicity-increasing amount of an antioxidant." Modifying Chinery to exclude the antioxidant would render Chinery unsuitable for its intended purpose of providing a combination comprising an antioxidant in order to "enhance the efficacy of antineoplastic drugs."

With respect to the secondary references, the Examiner cited D'Amato for the teaching that angiogenesis has been associated with rheumatoid arthritis, atherosclerosis and leukemia; Cecil for the proposition that there is no one particular antineoplastic agent or combination thereof that is known to be effective for the treatment of each and every type of cancer known; O'Dwyer for the teaching that homoharringtonine may be effective against leukemia; Medford for the teaching that atherosclerosis is an

inflammatory condition; and Powell II for the teaching "harringtonine, isoharringtonine, homoharringtonine and deoxyharringtonine were known in the art as being effective against leukemia," which as argued above, is too broad a reading of Powell II.

None of these secondary references cited by the Examiner provide a reason to exclude the use of an antioxidant when contacting a host with a cephalotaxine such that angiogenesis associated with an angiogenic disease is inhibited. Although angiogenesis may be associated with leukemia involving the bone marrow and homoharringtonine may be effective against nonvascularized leukemic cells, it does not follow that one of skill in the art would exclude the use of an antioxidant when contacting a host with a cephalotaxine such that angiogenesis associated with an angiogenic disease is inhibited. Indeed, none of the references teach that HHT or any cephalotaxine would inhibit angiogenesis associated with an angiogenic disease. The Examiner has not established why one of skill in the art would modify Chinery to exclude an antioxidant from combination therapy and then combine Chinery with the remaining references such that the claimed invention is obvious. Applicant therefore respectfully requests withdrawal of the rejection.

Conclusion

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1216 (direct line).

While Applicant believes that no fees are due at this time, the Commissioner is hereby authorized to charge any such fees, including extension fees, or any other relief that may be required, in connection with this reply to Deposit Account 50-0310 (Attorney Docket No. 067716-5012-US).

Respectfully submitted,

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